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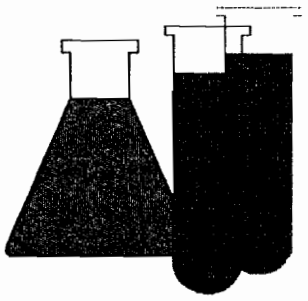

PESTICIDE REREGISTRATION AND QA: A SCIENTIST'S PERSPECTIVE

By Dr. Ray Sterner

Ray Sterner is Supervisory Research Psychologist (Animal Behavior) at the National Wildlife Research Center (NWRC) in Ft. Collins, CO. He currently supervises Biological-Chemical Effects Staff within the Product Development Section, and leads a project aimed at R&D of new rodent-repellent technologies. Ray is a member of RMRCSQA and current Chair of the Membership Committee; he finds membership useful as a source of GLP/QA training, plus "the people are great". This paper evolved from invited presentations at the October 1996 National SQA Meeting (Baltimore, MD) and the November RMRCSQA Meeting (Colorado Springs, CO) in which overviews of selected USDA/APHIS pesticide reregistration efforts were presented. Here, he gives his perspective on the conduct of pesticide registration and reregistration studies, as well as the challenges facing environmental scientists and QA professionals now that the initial surge of reregistration studies are nearing completion.

USDA/APHIS/ADC PESTICIDES

The U.S. Department of Agriculture (USDA), Animal Plant and Health Inspection Service (APHIS), and Animal Damage Control Program (ADC) maintains numerous Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Section 3 (federal) and 24c (local-use) pesticide registrations for the control of rodents and birds that damage crops, impact endangered species, or pose human-health risks. The NWRC provides scientific expertise and liaison within APHIS for maintenance of these registrations.

Altogether, 7 active ingredients (A.Is.) are involved: carbon, sodium nitrate, sodium cyanide, sodium fluoroacetate, 3-chloro-p-toluidine hydrochloride, zinc phosphide, and strychnine alkaloid. For example, 3 USDA/APHIS/ADC Section 3 registrations specify use patterns for 1% or 2% oat or wheat grain baits for the control of meadow voles and field mice in orchards, nurseries, etc. with the acute rodenticide zinc phosphide; reducing these rodent populations prevents tree destruction due to "girdling" -- the encircled removal of bark around trunks. Although sizable volumes of zinc phosphide are used annually, most registrations involve low-volume use pesticides (<50 kg/yr) -- chemicals that address a specific wildlife damage issue, but whose manufacturing costs are difficult to justify based on sales.

FIFRA-88: PESTICIDE REREGISTRATION

Under the Federal Environmental Control Pesticide Act of 1972, Congress directed The Environmental Protection Agency (EPA) to assess environmental safety/human hazards linked with chemicals dispensed throughout the US. Safety/environmental issues were to be resolved by 1977. The magnitude of this task, coupled with the "tiered-study" concept whereby observations of secondary toxicity, environmental persistence, etc. would "trigger" more in-depth research, slowed progress. Thus, in 1988, Congress amended FIFRA (FIFRA-88) to speed EPA's efforts.

FIFRA-88 mandated that all pesticides containing an A.I. registered prior to November 1, 1984 be "reregistered" within a 9-year period (by 1997). This involved 600 groups of Active Ingredients (A.Is.) and 45,000 formulated products (EPA, 1991). Coincident with this were EPA's own initiatives to implement 40 Code of Federal Regulations (CFR), Part 160 (October 16, 1989) -- the Good Laboratory Practices (GLP)/Quality Assurance Unit (QAU) regulations that many of us in RMRCSQA know so well (EPA, 1989). Parts 150-189 of 40 CFR specify the types of chemical environmental/human health hazards studies that can be required to register/reregister a pesticide. Twelve subdivisions (D through R) to "The Code" specify the types of data that can be required of a registrant for an A.I (e.g., D Product Chemistry, E Hazard Evaluation: Wildlife and Aquatic Organisms, F Hazard Evaluation: Humans and Domestic Animals, G Product Performance, etc.). Each of these subdivisions contains a matrix of the studies used to assess risks based upon a chemical's "general use pattern" [Terrestrial (Food/Non-food Crop); Aquatic (Food/Non-food Crop); Greenhouse (Food/Non-food Crop); Forestry; Domestic Outdoor; and Indoor) and "test substance" (Manufacturing-use Product or End-use Product); examples of Sub-division F Studies are: 81-1 Acute Oral Toxicity (LD_{50} Rat), 81-2 Acute Dermal Toxicity (LD_{50} Rabbit), 81-3 Acute Inhalation Toxicity (Rat), and 81-4 Primary Eye Irritation (Rabbit).

To implement FIFRA-88, EPA responded with a 5-phase plan:

Phase 1 (List A.Is.).-- By October 1989, EPA had issued Lists A, B, C, and D of A.Is. subject to reregistration. A total of 194 A.I.s (350 specific technical products) were on List A. Lists B, C and D then named 229, 288, and 286 pesticides (an additional 261 A.Is.), respectively, in descending order of expected environmental-/human-health risks -- a sort of "triage" approach to risks assessment.

Phase 2 (Declare Intent).-- By January 1991, companies that formulated, sold or manufactured the A.I. products had been afforded 90 days to notify EPA whether or not they would seek reregistration of an A.I. This also entailed a commitment to provide new GLP/QA studies (if needed) and pay fees for each chemical ($50-150k/A.I. plus $700/annum for the 1st end use product and $1400/annum for each additional such product) to be registered.

Phase 3 (Summarize Past Studies).-- By October 1990, registrants had provided summaries of past studies, reformatted data, and identified "adverse" data from prior studies bearing on diverse issues related to reregistration (e.g., efficacy, human health effects, environmental fate) of A.Is. Initial fees were also paid.

Phase 4 (EPA Reviews and Data Call-ins).-- By July 1992, EPA was expected to review the Phase 2 and 3 data. Data Call-ins for additional studies concerning a particular A.I. were issued, with a 4-year completion date imposed (1996).

Phase 5 (EPA Decisions).-- By December 1997, Registration Eligibility Documents (REDs) are to have been issued for the A.Is. EPA is expected to have reviewed all

of the submitted studies and decided whether or not to reregister the A.I. at this time. Studies that will be needed for reregistration of end-use products (the field formulations involving A.Is.) must be identified. [Note.-- At present, it is uncertain whether or not this deadline will be met; USDA/APHIS has received certain REDs, but others are still not issued.)

PERSPECTIVE ON 40-CFR STUDIES

Since 1988, USDA/APHIS/ADC has summarized, submitted, or received waivers for 500 studies needed to register/reregister the 7 A.Is. mentioned earlier. I have conducted or served as contract monitor for 16 of these Subdivision E, F, and G studies. This experience has afforded some insight into my own performance.

Conducting/monitoring mandated studies sought by EPA requires adherence to standard GDLNs published by this agency. Of course, the performance of any routine, standardized study is the bane of a scientist; it implies the conduct of non-creative, "canned" research. Well, forget that! The importance/expense of these studies offsets such negatives. That your data will be used to determine crop tolerances for safe human/animal consumption, to set aquatic usages in/near fisheries, to identify secondary hazards to nontarget wildlife, etc. constantly remind you of the critical nature of each study. Moreover, interpretation of often-vague guidelines (GDLNs), attention to enormous numbers of details (e.g., 90-day pre-/post-study technical product assays, timeliness of SOPs, evidence of training for all participants), and preparation of accurate complete reports/archives are not trivial. Providing data/reports/archives that comply with GLP and "weather" a QA data audit, not to mention a possible on-site EPA inspection and your potential defense of an archived study, requires a focus of detail and organization generally lacking from "basic" research. Combine these with the Study Director's responsibility for test systems -- animals -- [see CFR 9 (Parts 1-199); USDA, 1996] should dispel all complacency.

A personal example that will always remain fresh in my memory concerns monitoring the "Draize Test" (GDLN 81-4) for the A.I. 3-chloro-p-toluidine hydrochloride (Draize, Nelson, and Calvary, 1944). This test requires that a small amount of concentrated A.I. be placed into one eye of albino rabbits. The chemical is an avicide used to alleviate certain nuisance gull, blackbird (feedlot), and pigeon populations in the US; it is acidic.

My experience involved an unexpected phone call from the Study Director on Day 3 of the test. He informed me that "severe irritation" was present in several of the rabbits' eyes; "What do you want to do?" Well, the answer is easy today, you euthanize animals that appear to be in "severe pain"; but in 1990, EPA provided very little guidance regarding these types of things. The implication was that tests should "go to term" (14 days) so that results would not be compromised.

I elected to go several more days and have the Study Director "watch the situation"; however, on Day 8 (after multiple, daily communications) the study was stopped and the rabbits euthanized. To protect the data, my laboratory paid a Veterinary Ophthalmologist (a rare, highly paid specialist) to examine, photograph, and sign a clinical opinion that "irreversible corneal damage" had occurred to most rabbits' eyes.

Interestingly, the data submission was accepted without discrepancy. The RED document for the avicide came out last year, with an okay for reregistration, but required that the "PRECAUTIONARY STATEMENTS" contained in the upper right portion of this pesticide's "use labels" read as follows:

> "Harmful if swallowed, inhaled, or absorbed through the skin. Avoid contact with eyes, skin, or clothing. Handle only with protective gloves, clothing, and face

mask, or respirator. Wash hands with soap and water after handling."

For me, this is evidence that the reregistration process works effectively. The submission of negative data for 1 study did not condemn the avicide to non-reregistration status. Precautions reflected on the use label concur with results of the Draize Test. They warn human applicators of potential irritation (safety/health) effects, but also convey that risks to humans can be mitigated by proper handling of the chemical.

FIFRA-88 -- BOOM OR BUST FOR QA?

You may be surprised to learn that many RMRCSQA members owe their livelihoods to FIFRA-88. This legislation generated literally hundreds of QA jobs via numerous "start-up" laboratories seeking to contract and conduct the myriad of toxic-effects studies required to reregister pesticides. The relatively condensed timeline for these data submissions caused testing labs to flourish.

The 5 phases of FIFRA-88 are ending. Such an intense period of data submissions will probably not occur again. Environmental scientists and QA professionals working in this area need to be cognizant of the projected patterns of pesticide usage (world pesticide usage has stabilized at 800 million lbs. during the past 20 years) and manufacturers' plans for future chemical registrations/reregistrations. [Note.-- Of the 600 A.Is. cited in Phase 1 of FIFRA-88, 160 were cancelled due to inaction -- decisions not to pay the fees or costs of required studies for these chemicals].

From my perspective, this signals a time to examine the direction of chemical manufacturing, future product development, and environmental concerns of the US (and world) populace. Certainly, sale/use of toxic pesticides will decline. Many toxicology tests (such as The Draize) will be banned. These will be replaced by cell-culture-type tests shown to produce valid indices of toxicity/carcinogenicity; data from these will be counted/stored automatically by digitizing microscopes via computer links. Computerized models of potential chemical/biological/pharmacological effects will provide iterative datasets of possible outcomes that will serve as the assessment of environmental/human consequences. Biotechnology will produce pest-resistant, fast-growing, greater-yielding animals/plants.

What does this suggest? That's right -- "downsizing". Decreased reliance on traditional toxicology and environmental fate work that many of us have performed/checked is "on the agenda". Don't panic, it won't be tomorrow. May I suggest that you broaden your QA skills (always good advice). QA professionals knowledgeable of Good Automated Laboratory Practices (GALPs) and Good Clinical Practices (GCPs) should find a "hot" market for their skills. Software-based data management and QA-oversight/-security of these files will be essential -- become a "hack", you can do it. Of course, in the short-term (<10 years), clinical-type data collections for Investigational New Animal Drugs (INADs) or New Animal Drug Applications (NADAs) with Food and Drug Administration (see 21 CFR; FDA, 1996) will need to be performed to register increasing numbers of veterinary-pharmaceutic and -biologic products.

Yes, as the period of FIFRA-88 ends, it is time for environmental scientists, QA professionals, and even laboratory owners/directors to reflect on "where we've been", "where we're at", and "where we're going".

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